In Vivo and In Vitro Effects of Angiopoietin-Like Protein 4 in Rheumatoid Arthritis

AB0083

STUDY OF THE ROLE OF ANGIopoetiN-LIKE PROTEIN TYPE 4 IN METABOLIC DISORDERs CAUSED BY INFLAMMATION IN RHEUMATOID ARTHRITIS

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Background: None declared

Objectives: To assess the potential role of angiopoietin-like protein type 4 (ANGPTL4) in metabolic disorders caused by inflammation in rheumatoid arthritis (RA).

Methods: The study included 88 patients with significant RA, 64 patients with other rheumatic diseases (RD) (36 patients with osteoarthritis (OA); 28 patients with psoriatic arthritis (PsA)); 17 patients with ankylosing spondylitis (AS)); and 32 healthy individuals. Estimation of ANGPTL4 was carried out by enzyme immunoassay using the commercial test system “RayBio Human ANGPTL4 ELISA Kit” (RayBiotech, USA) in blood serum. Levels of ESR, CRP, RF, antibodies to cyclic citrullinated peptide (anti-CCP) and modified vimentin (anti-MCV) in the ELISA test were determined for all patients with RA.

Results: The level of ANGPTL4 in the blood serum of patients with RA was significantly higher than in healthy people (p < 0.001) and patients with other RD (p = 0.012 compared with OA; p = 0.046 with PsA; p = 0.008 with AS). ANGPTL4 indices in patients with RA correlated with the age of onset of RA (r = -0.658, p < 0.001), disease activity according to DAS-28 (r = 0.449, p = 0.001), level of education (r = 0.235, p = 0.029), dose of glucocorticoid hormones (r = 0.321, p = 0.009) and methotrexate (r = -0.496, p = 0.05), the presence of osteopenia (r = 0.44), signs of kidney damage - proteinuria (r = 0.309, p = 0.037) and hypoalbuminemia (r = 0.386, p = 0.022), as well as with CRP levels (r = 0.488, p = 0.003), ESR (r = 0.458, p = 0.002), serum vitamin D (r = -0.417) and urinary calcium when recalculated to creatinine (r = 0.797, p = 0.032).

Conclusion: Patients with RA showed a high frequency of insulin resistance (according to the HOMA-IR index) (1.27 [0.84–1.62] in patients with RA; 0.76 [0.44–1.02] in healthy individuals; p < 0.001) and the presence of coronary heart disease, as well as a positive correlation between disease activity (according to DAS-28) and insulin resistance (according to the HOMA-IR index) (p = 0.333).

High levels of C-reactive protein (p = 0.04) and serum ANGPTL4 levels (p = 0.042, compared with patients with RD without type 2 diabetes; p = 0.028, compared with healthy individuals) were determined in the group of patients with RA with the presence of type 2 diabetes. ANGPTL4 acts as an inhibitor of lipoprotein lipase. His contribution to the development of dyslipidemia in RA can be demonstrated by the results we obtained when comparing groups of patients with / without signs of metabolic syndrome (MS). A positive correlation between ANGPTL4 and triglyceride levels (r = 0.42, p = 0.018) was found. An increase in the level of ANGPTL4 in blood serum of patients with RA with MS (p = 0.027 compared with RA without MS) can predict the development of cardiac pathology in this group of patients.

Conclusion: ANGPTL4 is directly involved in the regulation of glucose homeostasis, lipid metabolism, and insulin sensitivity. Cardiovascular diseases associated with atherosclerosis, insulin resistance and metabolic syndrome are known as the most common extraarticular manifestations of RA; the study of the role of ANGPTL4 in metabolic disorders caused by inflammation can show a new direction in the development of laboratory and therapeutic technologies in RA.

Disclosure of Interests: None declared

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Rheumatoid arthritis - aetiology, pathogenesis and animal models

AB0082

INHIBITION OF TGFβ SIGNALING USING SB-505124 BLOCKS TH17 DIFFERENTIATION AND RESTORES THE TH17/TREG BALANCE IN VIVO, BUT DOES NOT SUPPRESS EXPERIMENTAL ARTHRITIS

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Background: None declared

Objectives: In this study we aimed to investigate the effect of inhibition of TGFβ signaling with the ALK5 inhibitor SB-505124 on human Th17 differentiation in vitro, on cytokine production by human rheumatoid arthritis (RA) synovial explants, and study the effects of local SB-505124 treatment in vivo during innate immune and Th17-driven experimental arthritis models.

Methods: Magnetic sorted naïve human T cells were differentiated into Th17 cells with CD3/CD28 activation beads, IL-2, TGFβ, IL-1β, IL-23, aIFNγ and aIL-4 for 6 days. Human RA synovial biopsies were cultured for 24 h/w/o SmM SB-505124, and supernatant was analyzed by Luminex. T cell-independent SCW arthritis and Th17-driven IL-1β/BSA arthritis were induced in C57Bl6, and mice were treated with SB-505124 by daily intra-articular injections from day 0-4.

Results: SB-505124 potently reduced human Th17 differentiation in vitro by decreasing IL-17 and RORγt gene expression and IL-17 protein production. SB-505124 significantly suppressed IL-6 and TNFα protein production by human RA synovial explants. In addition, SB-505124 inhibited acute joint inflammation during SCW-arthritis (T-cell independent model). Interestingly, SB-505124 reduced Th17 levels in draining lymph nodes (dLN) during IL-1β/BSA arthritis while increased levels of Tregs were observed. Surprisingly, despite this skewed Th17/Treg balance, this did not result in suppression of joint inflammation and destruction in this Th17-driven arthritis model, whereas anti-IL-17 antibody treatment showed significant therapeutic effects.

Conclusion: We revealed suppressive effects of SB-505124 on human Th17 differentiation and the Th17/Treg balance in arthritic mice. However, SB-505124 did not suppress joint inflammation and destruction. This indicates that despite the importance of TGFβ in Th17 differentiation, targeting TGFβ signaling is not enough to suppress experimental arthritis.

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